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Increased Modulation by Cognitive Control Region during fMRI Working Memory Task Suggest Inefficiencies in Network Connectivity in Children with ADHD

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THESIS

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ABSTRACT:

Attention Deficit / Hyperactivity Disorder is a neurodevelopmental disorder common among children and adolescent populations whose symptoms are believed to be caused by deficits in executive functioning processes such as working memory. Using fMRI analyses, differences in the modulatory influence exhibited by the dorsal anterior cingulate cortex (dACC) on cortico-striatal regions implicated in working memory (2-back) (Owen et al 2005) was assessed between children with ADHD (twenty-three participants; mean age 6 yrs: 6.4-14.9 yrs) and healthy controls (twenty-six participants; mean age 10.1yrs: 6.3-14.1 yrs). Modulatory influence is defined as the degree to which one region exerts control on another region and was investigated using the analysis tool Psychophysiological Interactions (PPI) (Friston et al. 1997). Results of second level analyses show an increased level of dACC modulation on target regions (parietal lobe, middle frontal gyrus, dorsal pre frontal cortex) in children with ADHD and suggest an underlying inefficiency in control network circuitry. Further investigation into network efficiency was conducted using performance (d') and latency response data. Statistical analyses of performance and latency response times show similar averages between groups and indicate children with ADHD were not compromised in their ability to complete the 2-Back task. This suggests the differential pattern of dACC modulation observed in children with ADHD is not driven by behavioral symptoms of the psychiatric disorder and allude to functional differences in network circuitry driving the apparent inefficiency. Our inefficiency hypothesis is consistent with other fMRI studies investigating working memory in subjects with ADHD. Future analyses using longitudinal studies of subjects may highlight potential developmental implications on the modulatory behavior of the dACC in children with ADHD.

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ACKNOWLEDGMENTS

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CHAPTER 1
INTRODUCTION

The introduction is two parts. Part 1 is intended to provide background on the childhood disorder Attention Deficit / Hyperactivity Disorder (ADHD) in respect to prevalence, treatment, and etiology; highlight developmental trends in children's brains regarding cognitive control and working memory; and explore the role of neuroimaging studies, specifically fMRI technique, in characterizing ADHD.

Part 2 provides information about my research project at BRAIN.

PART 1

Background

Attention Deficit Hyperactivity Disorder (ADHD) is a common neurobehavioral condition in children and adolescence characterized by symptoms of excessive restlessness, impulsivity, and inattention (Health 2008)**.** Although ADHD has been found to affect adult populations, it is widely recognized as a childhood psychiatric disorder. The American Psychiatric Association (American Academy of Child and Adolescent Psychiatry) states that approximately 3%-7% of school-aged children have ADHD; however, studies conducted using community samples suggest higher numbers.

Studies conducted by National Institute of Mental Health (Health 2008) show the most effective treatment for managing the symptoms of ADHD are drug treatment with

methylphenidate (Ritalin, Metadate, Concerta) combined with behavioral therapy. Many psychostimulants used to treat children with ADHD exhibit therapeutic effects by blocking the re-uptake of the neurotransmitter dopamine at the nerve terminals in the brain (Kuczenski and Segal 1997; Volkow ND 1998). Dopamine has many functions in the brain, including a large role in cognition and behavior. The ADHD medication amphetamine (Adderall, Dexedrine) improve dopamine neurotransmission by inducing reverse transport of dopamine from the pre-synaptic neuron into the synaptic cleft (Kuczenski and Segal 1997; Thomas J. Spencer 2006). It is believed increased levels of dopamine in particular regions of the brain, such as those associated with reward and motivation (the ventral striatium) and in the prefrontal cortex, can improve behavioral symptoms of inattention (Volkow, Wang et al. 2012). ADHD medications have proven to be effective in symptom management, though long term effects of these medications on developing brains is not fully understood.

The FDA's age approval for the ADHD medications Ritalin, Dextrostat, and Dexetrin are 3 years and older, while other medications are approved for ages 6 and older (Healthy 2008). In the past decade, controversy surrounding medicating the youth has increased among parents and scholars. The mechanistic and pharmacological similarity of ADHD psychostimulant medications to recreational drugs such as cocaine prompt investigation into the long-term effects of chronic methylphenidate treatment on the developing brains of children. As with any recreational drug, the abuse potential for individuals habitually taking ADHD medications presents another concern. Results of the 2011 Monitoring the Future study (National Institute on Drug Abuse), indicate amphetamines (Adderall,

Dexedrine) as the third most common non-medical drug used by high school students, following marijuana/hashish and alcohol (Johnston 2012).

Developmental Trends in Children and Adolescents

Understanding the etiology of ADHD is challenging given the early childhood morbidity and overlap with rapid developmental changes happening in children's brains. As the brain matures from infancy and into adulthood it undergoes a series of developmental changes that enable mature adult-level behavior. Early development is characterized by the acquisition of exogenous-driven behaviors (reflexive, automatic, stimuli-driven) whereas later periods of development are dominated by the refinement of endogenous-driven behaviors (voluntary, planned, goal-driven) (Luna 2009). The emergence of such e**ndogenous-driven behaviors** will have lasting effects on many behavioral processes affecting decision making including emotional and cognitive control (Luna 2009).

Central to endogenous-driven process are behaviors associated with **executive function,** including voluntary response inhibition and working memory performance monitoring (Luna 2009). The plasticity of the brain during this critical time allows for increased optimization of neuronal circuitry allowing for more integrated and efficient functional interactions between brain regions and characterizes healthy brain development (Durston and Casey 2006; Luna 2009). Deviations from this developmental pattern (described below) may compromise a network's ability to perform optimally in executive function tasks as adults, and may be an underlying cause of psychiatric morbidity.

Executive Function and ADHD etiology

Executive function (EF) is a broad term used to characterize a range of 'top-down' cognitive processes and allows for flexible, goal-driven behavior (Welsh and Pennington 1988). Many scholars believe the symptoms of ADHD arise from a **primary deficit in executive function domains** such as response inhibition, **working memory**, or an extended weakness (Pennington 1996; Barkley 1997)**.** Regions of the brain mediating executive function processes are arranged in highly integrated networks and become dynamic in response to a particular cognitive demand (de Marco, Devauchelle et al. 2009). Several regions of the brain are involved in EF including the dorsal anterior cingulate cortex (dACC).

The Dorsal Anterior Cingulate Cortex, Working Memory and Cognitive Control

Studies implicate the dACC as part of a **general control system** involved in coordinating processes during **cognition and working memory** (Pardo, Pardo et al. 1990; Barch, Braver et al. 1997; Carter, Braver et al. 1998) and in complex cognitive and attention processing such as facilitation of correct and inhibition of incorrect responses. (Badgaiyan and Posner 1998; Bush, Frazier et al. 1999). This is supported by a recent 2012 meta-analysis conducted by Niendam and colleges **(Niendam, Laird et al. 2012)** of 193 fMRI who observed a common pattern of dACC activation across all executive function domains. The maturation of cognitive control systems is crucial for the development of highly integrated brain functioning (Luna, 2009) as adults. Therefore, research providing

insight into whether dACC interactions are altered or intact in adolescents may indicate deviations in the natural developmental patterns of children with ADHD.

In any goal-oriented action performed by a subject, the brains ability to 'configure' itself to perform a task (Botvinick, Cohen et al. 2004) requires flexible and interactive interactions between executive function systems. The **working memory** system allows for the flexible manipulation of stored data and has more recently been defined as the processes by which a remembered stimulus is held "on-line" to guide decision making (Goldman-Rakic, Cools et al. 1996). A Meta-analysis of executive components of working memory (Nee, Brown et al. 2012) found extensive and overlapping recruitment in regions including the parietal cortex, middle frontal gyrus, and prefrontal cortex.

Neuroimaging and ADHD

The scientific community's understanding of ADHD neurology improved in the past decade because of advances in neuroimaging techniques. Neuroimaging studies enable in-vivo investigations of living subjects and make the brain more accessible to investigate structural and functional differences in neuronal systems. As a result, researchers can now attempt to illuminate neural mechanisms responsible for behavioral and performance deficits in individuals. Neuroimaging studies use images generated from techniques including positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) and often require subjects to perform a specific cognitive task during assessment. **Task-based designs** are useful in psychiatric studies because they can isolate specific cognitive processes linked to or modified by psychiatric morbidity

(Paloyelis, Mehta et al. 2007). Cognitive deficits in subjects with ADHD can be assessed by employing a task-based fMRI that engage regions of the brain required in working memory and EF.

Magnetic Resonance Imaging technique

Of the neuroimaging techniques available, Magnetic Resonance Imaging (MRI) allows researchers to map activated brain regions by exploiting the relationship between brain energy metabolism and cerebral blood flow (Logothetis 2002). Analytically, MRI is particularly useful in studying brain abnormalities because the images are of excellent contrast and high resolution. Thus, it is worth dedicating the next few paragraphs to explain the principles of MRI and a variant of this technique, functional MRI (fMRI), as it is commonly used to assess the integrity of neuronal systems in subjects with ADHD.

The principle behind MRI image production is best understood by breaking apart the name itself. Each component of Magnetic Resonance Imaging plays a critical role in producing a contrast image.

The Magnetic component of MRI refers to **two** separate magnetic scenarios that must interact in tissues to create contrast image signals. The first magnetic scenario is the presence, and later manipulation, of the natural magnetic field (dipole) created by hydrogen ions spinning on its axis in tissues. Hydrogen ions are particularly abundant in neuronal tissues making MRI technique especially useful in brain analyses. The second magnetic scenario refers to the external application of a high-strength magnetic field

inside the MRI column. This applied magnetic field is referred to as B0 and the strength of the magnitude typically ranges between 1.5T and 3T. To gain an appreciation for the strength of a 3T B0, in comparison to the Earth's magnetic field (5 x10-5 T), B0 is approximately 60,000x stronger.

The two magnetic scenarios interact when a subject is placed inside a MRI scanner and B0 is applied. When B0 is present, the randomly oriented proton dipoles in the tissue **align** longitudinally with B0 (either parallel or antiparallel). The net summation of the dipoles produces a net magnetization vector (NMV) and dictates the signal strength for image formation. The NMV does not create an image signal itself.

The Resonance component of MRI refers to the application of an **external frequency** that **resonates** with the natural frequency of the protons. The radio frequency is applied to manipulate the magnetic interactions between B0 and the proton dipoles. The radio frequency must resonate with the protons in order for the protons to absorb energy and shift their dipole direction into the transverse plane (away from the longitudinal plane with B0). When the applied radio frequency is removed, the protons emit the absorbed energy and relax back into longitudinal alignment with applied B0. During this 'relaxation' process an MRI signal is emitted by the protons and the signal is detected by a detector.
Depending on the type of tissues, the rates of realignment of the protons will vary and different contrast images can be generated.

In reference to the Imaging component of MRI, generating contrast images is a complex

process. Ultimately, image contrasts are made by varying the times between high frequency pulses and through different gradients along the magnetic field (Diwadkar and Keshavan 2002). Functional Magnetic Resonance Imaging (fMRI), a type of MRI, is a particularly useful for studying psychiatric disorders because it can be used to indirectly measure brain activity

Functional Magnetic Resonance Imaging (fMRI) and Brain Activity

Although brain activity cannot be measured directly, various metabolic and physiological principles allow researchers to collect indirect measurements. The metabolic demand of active brain tissue for oxygen is proportional with the level of activity. The brain responds to increased oxygen demands in tissues by increasing cerebral blood flow (CBF) to the needy region. This change in blood flow is known as the haemodynamic response (HR). fMRI technique detects HR changes in tissue using blood-oxygen-level-dependent contrast images (BOLD) that are made sensitive to changes in the oxygenation state of hemoglobin. Hemoglobin is the protein in red blood cells responsible for delivering oxygen throughout the body. Hemoglobin saturated with oxygen is called oxyhemoglobin and hemoglobin without oxygen is called deoxyhemoglobin. Deoxyhemoglobin is the imaging agent in fMRI because its paramagnetic nature is detectable by the fMRI detector.

Changes in the ratio of oxygenated/deoxygenated hemoglobin (oxy/deoxyHb) in brain voxels (an arbitrary volumetric unit) dictates how MR signals behave in BOLD images. Tissues with a large oxy/deoxy ratio will appear bright on BOLD images and indicate high levels of activity. (Le Bihan, Turner et al. 1993; Hyder, Shulman et al. 1998). It may seem

counterintuitive for activated neural tissue to have a high oxy/deoxyHb ratio because one would expect the large consumption of oxygen to decrease the ratio; however, physiological changes in blood flow throughout the brain mask this effect. In an effort to maintain the pressure gradient essential for the passive movement of oxygen into activated tissue, CBF to activated regions increases and results in a high oxy/deoxyHb ratio.

Once fMRI BOLD images are collected they are subject to statistical analysis using a variety of computer software. By analyzing changes in image brightness relative to a task being performed in the scanner, one can elude functional differences in working brains. These analyses are especially useful in cross-analyses comparing groups of subjects. The first step in fMRI cross-analyses is data processing followed by statistical parametric mapping (SPM). The following section will provide a brief overview of the steps involved in analyzing neuroimaging data and SPM.

Neuroimaging analyses

The aim of many neuroimaging studies is to characterize an observed fMRI response as being attributed to anatomical functional specialization, integration, or disease related effects in the context of an experimental demand, and moreover, test how well a proposed neurophsyiological hypothesis is modeled by the data. The process of analyzing neuroimaging data can be broken down into three main steps: (i) spatial processing, (ii) estimating parameters of a statistical model (statistical parametric

mapping), and (iii) making inferences about such parameters (Introduction to Statistical Parametic Mapping).

(i) Spatial processing

Spatial processing standardizes neuroimaging data by removing unwanted variances that may interfere with statistical analyses. Although there are several spatial processing steps, I will cover the basics of spatial realignment and normalization, and smoothing.

fMRI data is very sensitive to motion because of voxel displacement over a set of functional images. Spatial realignment is the process of removing unwanted variance cause by a subject's motion in a series of scans. Spatial normalization is performed after realignment and removes differences in brain morphology between individuals and translates an individual's brain onto a standard template. Smoothing is the final step in preparing neuroimaging data for analyses. During the smoothing process, a small "blurring" kernel is applied across the processed images to average part of the signal intensities from neighboring voxels. By improving the signal to noise ratio, smoothing attempts to establish a Gaussian noise distribution (random, independent between voxels and centered around zero) and therefore, increases the likelihood of extracting a signal resulting from a cognitive demand.

(ii) Statistical Parametric Mapping (SPM)

Functional mapping studies are commonly analyzed using SPM. Simply stated, SPM is a voxel-based analytical approach to make inferences about regional brain responses to an

experimental context. A SPM is constructed under the framework of the General Linear Model (GLM; Multiple Regression), linearly expressed as $Y= X\beta +\varepsilon$. Y (the observed response) corresponds to a set of functional images while X (the experimental variable) are conditions of an experiment.

(iii)Inferences

Once the SPM design matrix is built and processed images are assigned to the design, inferences about the functional implication of the neuroimaging data are explored using directional contrasts. Contrast (t- and f-contrast) inferences are used to determine regional effects induced by experimental conditions.

CHAPTER 1

INTRODUCTION

PART 2

Research Project

It is of significant value to investigate whether executive functioning systems are altered or intact in children with ADHD because psychiatric morbidity overlaps critical developmental periods responsible for the maturation of cognitive control systems. It is widely reported that subjects with ADHD are at a higher risk to engage in risky behaviors such as drugs use and sexual activities (August, Winters et al. 2006; Winters, Botzet et al. 2008) and have low academic performance, income, and poor social relationships. Identifying a neural basis, such as a dysfunction in executive function network connectivity, in subjects with ADHD may improve our ability treat those individual and better prepare them to live successful lives.

The purpose of my research project was to analyze fMRI using the analytical tool, psychophysiological interaction (PPI) to investigate the **modulatory influence** of the dorsal anterior cingulate cortex (dACC), on regions of the brain involved in **working memory** in children with ADHD, relative to healthy controls. Modulatory influence is defined as the degree to which one brain region exerts control on another region and is exhibited by a "seed region" onto 'target regions' in the context of a PPI (described below). We chose the dACC as our **seed region** because it is established as part of a general control system responsible for mediating cognitive control processes such as working memory (Pardo, Pardo et al. 1990; Barch, Braver et al. 1997; Carter, Braver et al.

1998) and because the dACC has extensive anatomical and functional connections with executive networks (Vincent, Kahn et al. 2008; Cools and D'Esposito 2011). We assigned the parietal lobe, dorsal prefrontal cortex, and middle frontal gyrus as target regions because they are associated with working memory operations believed to be altered in subjects with ADHD.

The **MATERIALS AND METHODS** section will provide an overview of the task used to assess and engage working memory system, what a PPI is, and processing information.

CHAPTER 2

MATERIALS AND METHODS

BACKGROUND

2-Back Working Memory Paradigm

Children in this study performed a 2-Back task while under fMRI assessment. 2-Back task requires the active monitoring, updating and manipulation of remembered information and therefore engages the neural basis of working memory. A meta-analysis of twenty-four **n-back** studies showed six cortical regions consistently activated including regions within the dorsal anterior cingulate cortex, parietal cortex, and dorsolateral prefrontal cortex (Owen, McMillan et al. 2005).

In this particular 2-Back task, subjects were shown a series of letters one-by-one on a screen and were instructed to respond to a letter when, and only when, the letter shown is the same as what was shown 2 probes earlier (Figure 1).

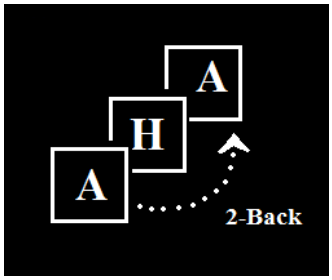

Figure 1: A correct response in a 2-Back task.

Psychophysioloical Interactions

Using the analysis tool, psychophysiological interactions (Friston, Buechel et al. 1997), differences in the modulatory influence exhibited by the dACC on target regions. PPIs are models constructed from a subject's fMRI series and combine information about activity in the dACC (seed region) and information about the externally applied stimuli (the 2-Back task). By making inference with PPIs, we can identify regions of the brain that respond to the stimuli when, and only when, activity in the seed region is high. On this foundation, we can infer that the seed region is modulating the response of these regions to the applied stimuli (Friston, Buechel et al. 1997).

The potential importance of PPI analyses stand on two notions. The first notion is that brain regions possess functional specificity, meaning regions become dynamic under specific cognitive demands. Therefore, observed regional interactions in PPI analyses are necessary to execute the specific cognitive demand. The second notion is that the response of a target region to an experimental stimuli is dependent on the contribution of the seed region on the target regions. This is referred to as the "contribution dependent change" by Friston and colleagues and implies that the seed region will exhibit a difference modulatory influence on target regions with different experimental stimuli.

fMRI collection and processing

Functional magnetic resonance imaging was conducted using Siemans3T running the Siemens Syngo console at the Vaetkiveckius Imaging Institute in the Wayne State University School of Medicine. Two 7-min gradient echo planar images were acquired using an 8-channel head coil (TR: 2.6 s, TE: 29 ms, matrix: 124 x123, 36 slices, voxels:

2x 2x3 mm). The fMRI time series consisted of 90 images. Images were preprocessed in SPM[R1] 8 (Statistical Parametrical Mapping, Wellcome Department of Imaging and Neuroscience, London, UK). The images of the fMRIs were oriented along the AC-PC line, then corrected for head movement. The images were spatially normalized to the MNI (Montreal Neuroscience Institution) template brain, and then were filtered through a high pass filter (256s)[R2] to remove low frequency components. Images were smoothed using a Gaussian filter (6 mm full-width half maximum; FWHM). An AR(1) model was used as an autoregressor for serial regression, and regressors modeled as a 30-s box-car vectors (for each of the task-related conditions) were convolved with a canonical hemodynamic response function.

ANALYSES

ADHD > HC Contrast

Twenty-six healthy controls (HC: mean 10.1yrs: 6.3-14.1 yrs) and twenty-three ADHD (mean: 9.6 yrs: 6.4-14.9 yrs) participated. Subjects performed four rounds of 2-back (36s) blocks interpersed with rest blocks (20 sec). fMRI data was subject to statistical analysis using SPM8. The modulatory influence of the dACC was investigated using psychophsiological interaction regressions created by convolving the time series (effects of interest, $p < 0.05$) with the psychological contrast (2Back>rest) (Friston, Buechel et al. 1997). Group differences (ADHD>HC) were assessed in 2nd level analyses with IQ, age, and gender as orthogonolized non-interest co-variates.

Performance Regression

Seventeen Healthy Controls (HC: mean 10.5 yrs: 6.3-14.0yrs) and eighteen ADHD (mean: 9.9 yrs: 6.4-14.9yrs) participated. Subjects performed four rounds of 2-back (36s) blocks interpersed with rest blocks (20 sec). fMRI data was subject to statistical analysis using SPM8. Performance regression was created for each group using d prime (d') values in 2nd level analyses.

Latency Regression

A latency regression was constructed using average latency response times to correct responses from seventeen HC (HC: mean 10.5 yrs) and sixteen children with ADHD (ADHD: mean 10.0 yrs). Latency response times for each subject were averaged for analyses and a regression was created for each group.

All analyses were spatially thresholded to the dorsal prefrontal cortex (dPFC), the parietal lobe (PAR), basal ganglia (BG), and middle frontal gyrus (MFG) using established automated methods (Maldjian et al., 2003). Cluster-level correction was applied using Alphsim (Ward, 2000) to correct for multiple comparisons.

CHAPTER 3

RESULTS

ADHD > HC Contrast

The ADHD>HC contrast image (Figure 2) shows regions of the brain that have increased dACC modulation in ADHD subjects *and* decreased dACC modulation in Healthy Controls (HC). Figure 2 shows increased dACC modulation in subjects with ADHD across the parietal lobe (peak cluster, KE= 711 voxels), MFG (peak cluster, KE= 331 voxels), and dPFC (peak cluster, KE= 178) relative to healthy controls.

Performance Regression

The performance regression was created to see if performance predicted dACC modulation. The performance value, or d prime (d'), is a statistic used in signal detection and calculates a subjects' discriminatory ability using discriminatory outcome rates as variables. This variable includes hit (responding to stimulus), miss (not responding to stimulus), false alarm (responding to no stimulus), and correct rejection (not responding to no stimuli). A higher d' value indicate a higher level of performance. Results of the performance regression show no significant correlation between dACC modulation and d' values between groups (HC: mean 2.38 range: 1.4-3.0; ADHD mean 2.0 range -1.0-3.3).

Performance Latency

A Performance Latency regression indicats whether a correlation exists between the level of dACC modulation and a subject's response time to the 2-Back stimuli. Relative to HC,

results show significantly less dACC modulation as latency **increases** in ADHD subjects (HC latency mean: 0.73; ADHD latency mean: 0.75) across parietal lobe, MFG, dPFC and PAR (Figure 3 and 4).

FIGURES

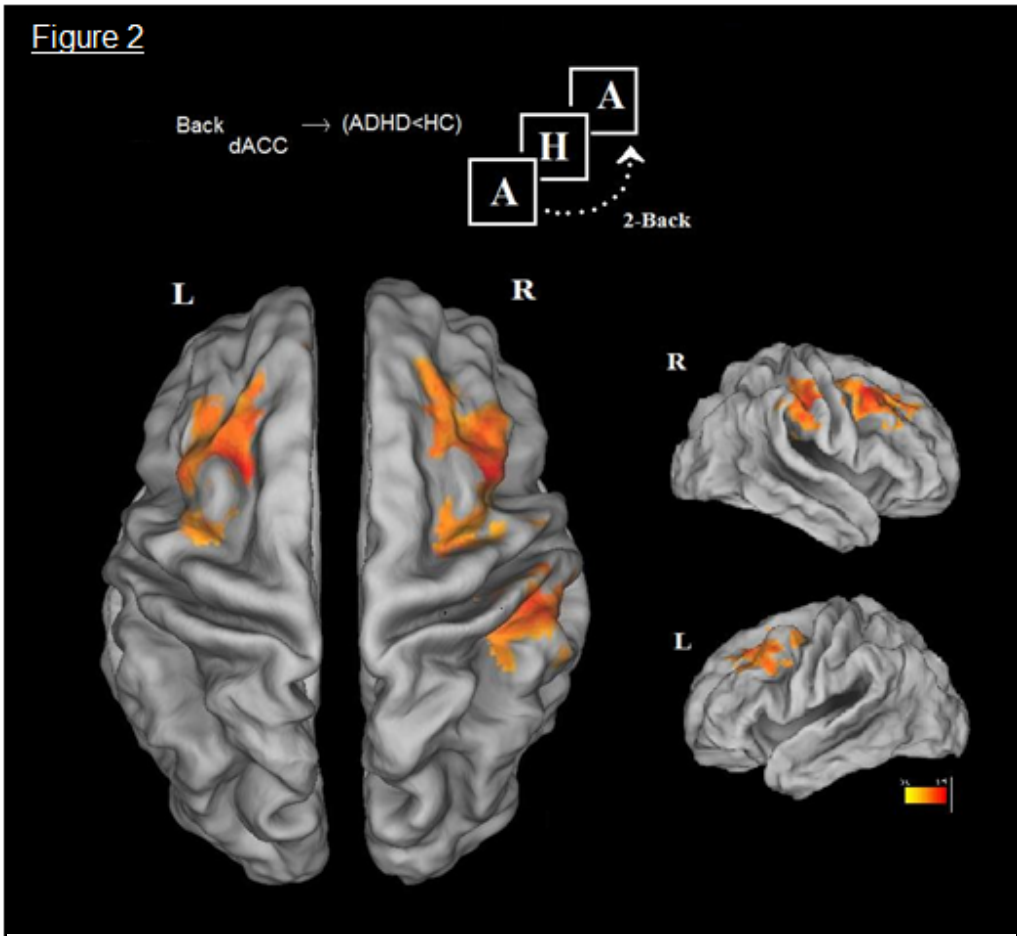

Figure 2: Corrected dorsal(L) and lateral (R) images (p<0.05) shows increased dACC modulation in ADHD>HC in the MFG, PAR, and dPFC

Table 1

Regions of Interest

Analyses	Location	t	Cluster Extent	Peak x	y	z
ADHD>HC	Middle Frontal Gyrus	3.67	331	-48	12	48
	Parietal Lobe	3.23	711	58	-24	45
	dPFC (BA 9 & 46)	2.98	178	46	13	40
Latency Regression Positive						
Healthy Controls	Middle Frontal Gyrus	3.43	263	-42	42	28
	Parietal Lobe	3.91	800	6	-70.5	54
ADHD	dPFC (BA 9 & 46)	3.54	170	15	59	34
	Middle Frontal Gyrus	3.72	266	-22	66	10
	Parietal Lobe	3.31	678	45	-61	45
	dPFC (BA 9 & 46)	3.31	134	44	46	9

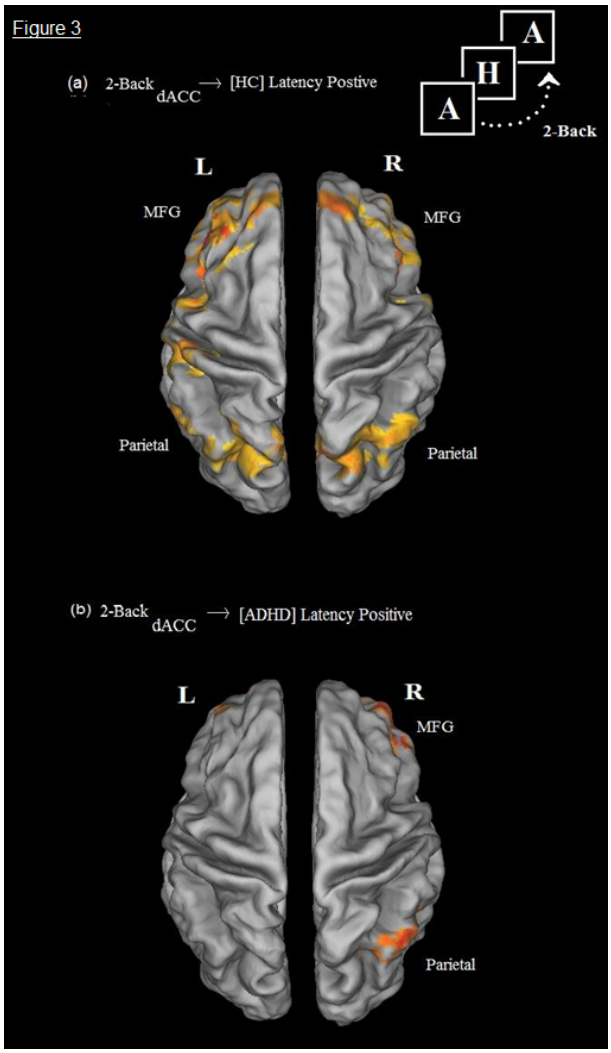

Figure 3 Dorsal View: dACC Modulation as latency response time increases. (a) Shows increased dACC modulation on MFG, Parietal regions in controls (b) shows significantly less dACC modulation in children with ADHD.

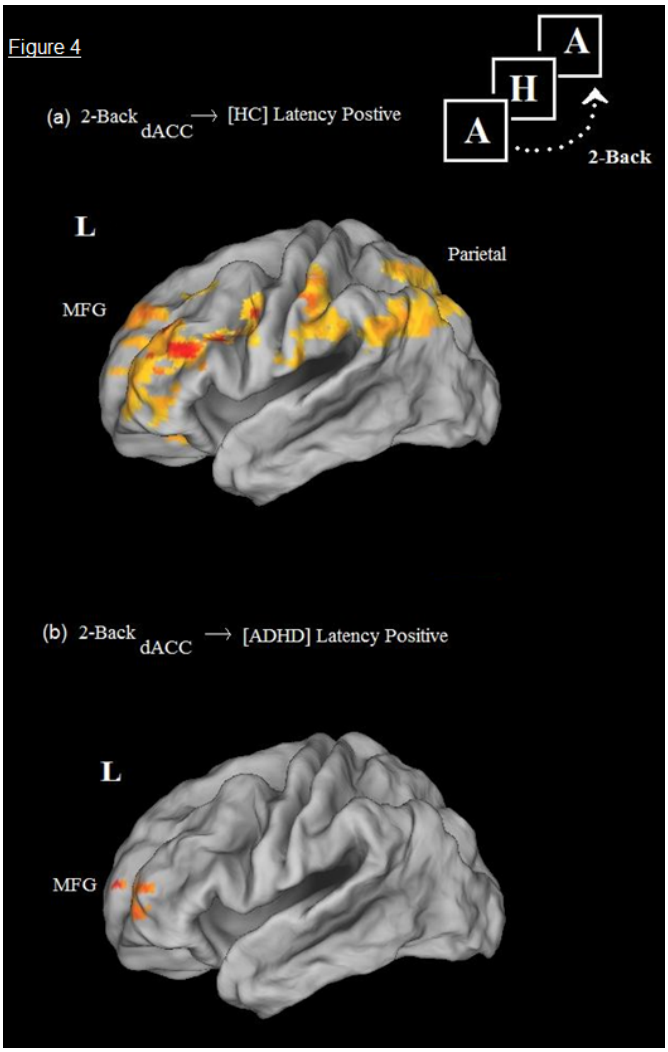

Figure 4 Lateral View: dACC Modulation as latency response time increases. (a) Shows increased dACC modulation on MFG, Parietal regions in controls (b) shows significantly less dACC modulation in children with ADHD.

CHAPTER 5

DISCUSSION

The purpose of my research project was to explore the modulatory influence exhibited by the dorsal anterior cingulate cortex (dACC) on parietal and cortico-striatal regions implicated in working memory in children with ADHD. Our results show an increased level of dACC modulation on target regions in children with ADHD which may be interpreted as the dACC requiring a higher level of control on target regions to execute the working memory task. We hypothesize the increased level of dACC modulation in subjects with ADHD reflect a latent inefficiency in control network connectivity. We attempted to characterize the apparent network efficiency in future analyses using performance and latency response data.

First, we investigated network efficiency from a behavioral perspective because we wanted to see whether the apparent inefficiency is a result of an underlying inefficiency in dACC connections to target regions or if functional results are driven by behavioral symptoms of ADHD while in the scanner. Differences in performance (d') could be attributed to behavioral symptoms of ADHD (inattention) interfering with a subject's engagement in the task and is likely to influence the dACC's modulatory behavior. A statistical analysis of d' values showed no significant difference in d' scores between groups which indicates both performed equally well on the task (HC: 2.38; ADHD: 2.0).We then created a performance regression to see if performance predicted a level of dACC modulation. Our results show no significant correlation between a subject's

performance score and the level of dACC modulation in both groups and suggest that the apparent inefficiency is not driven by behavior.

We then analyzed latency response time (LRT) data because latency (the time it takes to respond to a stimulus) is reflective of overall task efficiency. A statistical analysis of LRT show similar averages between groups and support performance analyses by demonstrating that group status does not affect a subjects' ability to do the task. A LRT regression was created to see if task efficiency was predictive of a level of dACC modulation. Our results show latency is predictive of dACC modulation in both groups; however, the direction of modulation differs as latency response time increases. In controls we see an increase in dACC modulation as LRT increases, while in ADHD group we see a decreased level of dACC modulation. These results suggest the neuronal circuitry executing working memory functioning configure differently in controls compared to subjects with ADHD. Moreover, these results increase the likelihood that underlying network inefficiency in subjects with ADHD is again responsible for the group's differential pattern of modulation from controls in the latency regression.

In conclusion, our research characterized significant differences in the modulatory behavior of the dACC in children with ADHD during a working memory task and suggests an underlying inefficiency in control network circuitry. Our inefficiency hypothesis is consistent with other fMRI studies investigating working memory in subjects with ADHD. Inefficiencies in functional recruitment was demonstrated in children with ADHD performing a *visual series addition task* (Fassbender, Schweitzer et al. 2011) which

showed reduced brain activation across working memory domains, relative to HC. In addition, functional connectivity abnormalities and localized brain activation deficits were observed in adults with ADHD during a verbal working memory task across several working memory domains (Wolf, Plichta et al. 2009). Moreover, Wolf and colleges found no significant difference in behavioral performance between groups.

It is possible that the increased level of dACC control on working memory domains may be a plastic response functioning as a compensatory mechanism to meet the cognitive demands in an otherwise ill-prepared regional circuitry. This idea is supported by a study conducted be Burgess and colleges (Burgess, Depue et al. 2010) who investigated whether a subject's working memory *ability* could explain differential brain activation patterns in adults with ADHD and controls during an *attention demand task*. Their results suggest that a low working memory ability may prevent subjects with ADHD from maintaining attention to the task at hand (indicated by *decreased* activation levels) and moreover, hypothesize that the observed *increased* recruitment of stimuli-driven attention and response selection processes associated with a high working memory ability may be a compensatory mechanism in subjects with ADHD. To date, there are no fMRI studies to my knowledge using latency response regression to characterize working memory deficits in individuals with ADHD. In the future, it would be interesting to see if there are any long-term developmental effects on the modulatory behavior of the dACC in children with ADHD using longitudinal studies.

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